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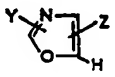
(72) Inventor KEVAN BROWN

(54) OXAZOLES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

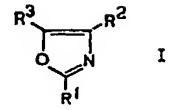
This invention relates to a novel group of oxazoles containing an aliphatic acid residue or a derivative thereof in the 2-position, to processes for the preparation thereof, and to pharmaceutical compositions containing such compounds.

U.K. Specification No. 1,139,940 claims an oxazole derivative of the formula:—



wherein Y stands for a phenyl or benzyl radical, either of which may optionally be substituted in the benzene ring by not more than two halogen atoms or by the trifluoromethyl radical, and Z stands for a group of the formula $—CR^1R^2R^3$, wherein R^1 stands for hydrogen or an alkyl radical of not more than 3 carbon atoms and R^2 stands for hydrogen, an alkyl radical of not more than 3 carbon atoms, or an alkoxy-carbonyl radical of not more than 6 carbon atoms, and R^3 stands for a group of the formula $—CO_2R^4$ or $—CONHR^5$, wherein R^4 stands for hydrogen or an alkyl, dialkylaminoalkyl, benzyl or phenyl radical, and R^5 stands for hydrogen or a hydroxy, amino dialkylaminoalkyl, alkoxycarbonylalkyl or carboxyalkyl radical, or a salt thereof.

The present invention provides oxazoles of the general formula:—



I

and acid addition salts thereof, in which R^1 is a saturated or unsaturated aliphatic carboxylic acid residue containing from 2 to 6 carbon atoms or a salt, ester, amide or hydroxamic acid derivative thereof, said carboxylic acid radical or salt ester, amide or hydroxamic acid derivative being attached to the oxazole ring by a carbon atom of the aliphatic chain, at least one of R^2 and R^3 is a substituted or unsubstituted aryl group (which may be a heteroaryl group) and the other radical R^2 or R^3, if not a substituted or unsubstituted aryl group (which may be a heteroaryl group), is a hydrogen atom or an alkyl group with the proviso that when R^3 is a hydrogen atom and R^2 is a phenyl radical which may optionally be substituted by not more than two halogen atoms or by a trifluoromethyl radical, then R^1 contains at least two carbon atoms in a straight chain between the oxazole ring and the carboxyl group or salt, ester, amide or hydroxamic acid derivative thereof.

The radicals R^2 and R^3 sometimes may be the same and preferably are both monocyclic or bicyclic aromatic carbocyclic radicals (such as phenyl or naphthyl radicals) or heterocyclic aromatic radicals (such as thienyl or furyl radicals), any of which radicals may be substituted, but for simplicity all such aromatic radicals are referred to herein as aryl radicals. The aliphatic acid residue, or derivative thereof R^1, can be saturated or unsaturated, straight or branched chained and advantageously contains 2 to 4 carbon atoms.

The compounds of the above general

[*Price 5s. 0d. (25p)*]

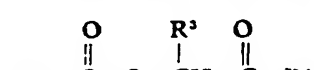
formula exhibit pharmacological activity, for example anti-inflammatory activity, as shown by tests on laboratory animals, or are intermediates in the preparation of other substituted oxazoles.

The compounds of the above general formula may be prepared by suitable general methods known for forming an appropriately substituted oxazole ring. Such methods are well known, see for example "Heterocyclic Compounds", Volume 5, by Robert E. Elderfield, 1957, published by Wiley and Sons, pages 302 to 323. The invention therefore also provides a process for preparing an oxazole of the above general formula, which comprises cyclising one or more reactants appropriately substituted by radicals R^2, R^3 and R^4 (where R^2 and R^3 have the meanings defined above and R^4 has the same meaning as R^1 or is a radical convertible thereto) to form an oxazole of general formula I in which R^1 is replaced by R^4, and if necessary converting radical R^4 to R^1.

The radicals R^2 and R^3 preferably are both aryl radicals, which may be the same or different, for example phenyl, naphthyl, thienyl and furyl radicals. Examples are unsubstituted phenyl, phenyl substituted by halogen (e.g. fluorine, chlorine, or bromine), by lower alkyl radicals containing up to 6 and preferably up to 4 carbon atoms (e.g. methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl and *iso*-butyl), by lower alkoxy radicals containing up to 6 and preferably up to 4 carbon atoms (e.g. methoxy), by alkylsulphonyl, by alkylthio, by trifluoromethyl radicals, by nitro, by amino, particularly dialkylamino (e.g. dimethylamino) or substituted or unsubstituted naphthyl, thienyl or furyl radicals (e.g. 1- or 2-naphthyl, 2- or 3-thienyl or 2- or 3-furyl.) If desired, a phenyl ring may contain two substituents (e.g. methyl and chlorine), though generally only one substituent at the most is present. However, one of the radicals R^2 and R^3 can be a hydrogen atom or an alkyl radical (e.g. a methyl radical).

The radical R^1 is an aliphatic carboxylic acid radical containing 2 to 6, preferably 2 to 4 carbon atoms, or is an ester, amide or hydroxamic acid derivative. The radical R^1 generally is in the acid form and examples of such acid radicals are those derived from acetic, *n*-propionic, *iso*-butyric, valeric or an ethylenically unsaturated acid such as acrylic acid. On the other hand, whereas R^4 generally is an acid radical or ester derivative thereof, R^4 may also for example be a cyanoalkyl, hydroxyalkyl or haloalkyl radical or other radical convertible directly or indirectly to an acid radical, and after the oxazole ring has been formed the radical R^4 can be converted to the acid form or to one of the above-defined derivatives thereof, either directly or after passing through the acid form. It is frequently possible for example to convert a haloalkyl (e.g. chloromethyl) derivative to the acid by reaction with an alkali metal cyanide (e.g. sodium or potassium cyanide) or by reaction with an alkali metal derivative of a diester, followed in either case by hydrolysis. Similarly R^4 may be a $—CO_2H$ radical which may be converted to R^1 by an Arndt-Eistert reaction.

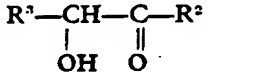
A convenient general method for preparing the oxazoles of general formula (I) is based on Davidson's oxazole synthesis and comprises reacting a keto ester of the general formula



(II)

with a nitrogen-donating cyclising agent, for example with ammonia or a salt thereof or with urea (in which formula R^2, R^3 and R^4 have the meanings defined above). This reaction can be carried out with or without the use of a solvent. If a solvent is used, heating in solution from elevated temperature up to the boiling point of the solvent, for example, under reflux, is convenient. The use of urea is generally preferred to the use of ammonia or an ammonium salt (for example ammonium acetate in glacial acetic acid) as the product is easier to work up. The compound of general formula II used in the cyclisation reaction preferably contains a radical R^4 which is in the free acid form. Examples of such compounds are the hemisuccinate and hemiglutarate esters of benzoin, ω-hydroxyacetophenone and α-hydroxybenzaldehyde and of derivatives thereof in which the benzene rings are substituted.

The keto esters of general formula (II) can be prepared by esterifying an α-hydroxyketone of general formula



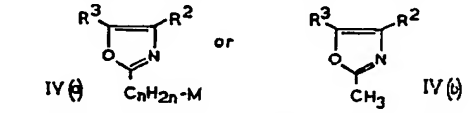
(III)

or a corresponding compound in which OH is replaced by halogen (e.g. bromine) with a suitable reagent capable of converting the OH or halogen group to an α—O—CO—R^4 group, or a group itself convertible to an α—O—CO—R^4 group. For example, (a) the esterification can be carried out on the OH group of the compound of general formula II with an appropriate anhydride, acid, acid halide, or other esterification agent, or (b) the halo group can be reacted with the monoalkali metal salt of the acid. It is very convenient to use the acid anhydride, (for example succinic, glutaric or maleic anhydride) or the corresponding acid chlorides to acylate the hydroxy group.

The esterification can be carried out by heating the reactants together at elevated temperature either in solution or in a sealed tube.

Temperatures of up to 180°C generally are suitable, for example 100—140°C. When an inert organic solvent is used, (e.g. a hydrocarbon) the esterification can be effected under reflux.

A less preferred method of preparation of compounds of general formula I in which R^1 is a saturated aliphatic acid radical comprises forming an oxazole of general formula

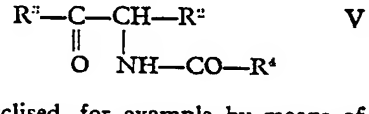


IV(a) IV(b)

in known manner (in which R^2 and R^3 have the meanings defined above, n is a whole number from 1 to 5 and M is an alkali metal atom) and converting the 2-substituent to the desired acid. Thus the compound of formula IV(a) can be reacted with a haloaliphatic acid ester, followed by hydrolysis. The compound of general formula IV(b) can be halogenated and then reacted with a nitrile or malonic ester, followed by subsequent hydrolysis. Alternatively, the compound of general formula IV(b) can be converted to the corresponding 2-formyl derivative by means of a Sommelet reaction, and this aldehyde subjected to a Knoevenagel or similar reaction with a malonic ester to give the acrylic derivative which may be reduced to the propionic derivative.

The following less-preferred methods of preparation, known for the preparation of oxazoles can, if necessary, be used for the preparation of the novel oxazoles of general formula I, R^2, R^3 and R^1 having the meanings defined above.

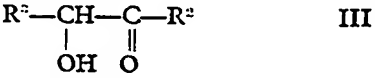
A) Following the Robinson-Gabriel synthesis, an α-acylamino ketone of the general formula



V

can be cyclised, for example by means of a cyclising agent such as sulphuric acid, phosphorus pentachloride, phosphoryl chloride or phosphorus pentoxide.

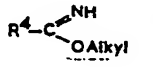
B) following Japp's synthesis, a hydroxy ketone of the formula



III

can be reacted with a nitrile of formula R^4CN.

C) An imino ether of general formula



VI

can be reacted with an α-amino ketone, or a salt thereof, of the general formula

VII

e.g. in hot acetic acid. The starting material of general formula VI can be prepared by forming the iminoether of benzoyloxymethyl nitrile.

The actual method of preparation to be used for preparing a particular compound will depend on the compound in question, and the most suitable method advantageously is used in any particular case.

The starting materials for the above processes generally are known or can be obtained in analogous manner to methods for preparing similar known compounds. If the product obtained after carrying out one of the above-mentioned processes is not that desired but a derivative thereof, it can be converted to the desired compound in known manner e.g. following the information given below.

It is apparent in any of the foregoing reactions that if substituents are present in the aryl rings they must be inert under the reaction conditions, if necessary by being blocked by standard methods while the reaction is being carried out and only formed after a compound of general formula I has been produced. For example, an amino radical can be blocked in known manner (e.g. with an acylating agent) and the blocking agent removed once the oxazole has been formed.

If the product obtained after carrying out one of the above-mentioned processes is not that desired but a derivative thereof, it can be converted to the desired compound in known manner. For example, a nitrile can be hydrolysed to the acid or amide; an ester can be hydrolysed to the acid or converted to the hydroxamic acid derivative by reaction with hydroxylamine; and acyloxymethyl ester can be prepared from the acid or a salt thereof by reaction with an acyloxymethyl halide; and an amide preferably is prepared by reacting the acid with an alkyl haloformate followed by reaction with ammonia.

As the compounds of general formula I contain a basic nitrogen atom, they can form salts with pharmaceutically acceptable acids, (though they are easily hydrolysed back to the free base), and the invention also provides such salts.

The invention further provides a pharmaceutical composition, which comprises a pharmaceutically active form of a compound of general formula I provided by the invention, which may be micronised, and a non-toxic carrier. The pharmaceutically active form generally is when R^1 is a carboxylic acid group, which may be in salt, ester or amide form.

The carrier can be solid, liquid or a mixture, e.g. a cream, any suitable carrier known in the art can be used and the particular carrier chosen will depend on the compound, the effect desired and standard pharmaceutical practice.

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

β-(4,5-Diphenyloxazol-2-yl)propionic acid

(a) Benzoin (21.2 g.) and succinic anhydride (10.0 g.) were heated together at 120°C for 6 hours. After cooling, the glass-like solid formed was dissolved in ether, and extracted with dilute aqueous sodium carbonate solution. The basic extract was washed once with ether, and then acidified with hydrochloric acid. The resulting oil was extracted with ether and the extract washed with water, dried over Na_2SO_4, and evaporated to give an oil which solidified to form prismatic crystals of benzoin hemisuccinate ester (27 g., 87%), m.p. 86—88°C. An analytical sample was recrystallised from aqueous acetone to give prisms, m.p. 88.5—89.5°C.

(b) Benzoin hemisuccinate ester (15 g.) and ammonium acetate (30 g.) were heated in refluxing glacial acetic acid (100 ml.) for 1½ hours. After cooling, the solution was poured into water, and the resulting crystalline precipitate was filtered off, washed with water, and recrystallised from methanol to give needle-like crystals of β - (4,5 - Diphenyloxazol-2-yl)propionic acid (11.7 g., 83%), m.p. 160.5—161.5°C.

Analysis: Found: C, 73.9; H, 5.4; N, 5.0. $C_{18}H_{15}NO_3$ requires C, 73.8; H, 5.2; N, 4.8%.

EXAMPLE 2

β-[4,5-Di-(4'-methoxyphenyl)oxazol-2-yl]propionic acid

(a) Anisoin (13.6 g.), succinic anhydride (5.5 g.) and toluene (3 ml.) were heated with stirring such that the internal reaction mixture temperature was 135—140°C for 5 hours.

The mixture was allowed to cool, ether (100 ml.) was added and the insoluble succinic anhydride removed by filtration. The filtrate was added to stirred 0.5N sodium bicarbonate solution (250 ml.), the organic layer was separated and was extracted with further 0.5N $NaHCO_3$ solution (2×50 ml.). The combined aqueous layers were extracted once with ether (250 ml.) and acidified with concentrated HCl. The liberated oil was extracted into ethyl acetate (1×100, 2×50 ml.); and the combined organic phase washed well with water, dried ($MgSO_4$) and evaporated in vacuo to give a sticky foam of anisoin hemisuccinate. Yield 8.28 g. (44.4%).

(b) Anisoin hemisuccinate (5.52 g.) and urea (2.05 g.), in glacial acetic acid (30 ml.) were heated under reflux for 3 hours. The mixture was cooled and poured into ice/water (500 ml.). The liberated oil was extracted into ethyl acetate (3×150 ml.). The combined organic phases were washed with water until the washings were essentially neutral and then extracted with 0.5N sodium bicarbonate solution (3×75 ml.). The combined aqueous extracts were extracted with ethyl acetate (100 ml.), acidified with concentrated HCl and the resulting oil extracted with ethyl acetate (3×100 ml.). After washing with water, drying ($MgSO_4$), removal of the solvent yielded a sticky solid (3.96 g.). Recrystallisation from benzene/petrol (60—80) yielded tan-coloured crystals of the title substance. Yield 2.65 g. (50.7%), m.p. 78—82°C.

A sample recrystallised for analysis (from benzene) had m.p. 81.5—84°C.

Analysis: Found: C, 67.8; H, 5.8; N. 4.0%. $C_{20}H_{19}NO_5$ requires C, 68.0; H, 5.4; N, 4.0%.

A further sample was converted to the sodium salt by neutralisation with sodium hydroxide.

EXAMPLE 3

β-[4-(4'-Methoxyphenyl)-5-phenyloxazol-2-yl]propionic acid

The procedure of Example 2(a) was followed, but 4-methoxybenzoin (12.1 g.), (i.e. the ring adjacent to the keto group is substituted) and succinic anhydride (5.5 g.) were reacted for 5 hours at 135—40°C to obtain 4-methoxybenzoin hemisuccinate. Yield 10 g. (58.3%).

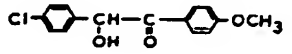
The procedure of Example 2(b) was then followed, but using this hemisuccinate (8.6 g.), urea (3.6 g.) and glacial acetic acid (25 ml.) to give the title compound. Yield 6.1 g. (75.1%), m.p. 118—20°C.

Analysis: Found: C, 70.5; H, 5.4; N, 4.5. $C_{19}H_{17}NO_4$ requires C, 70.7; H, 5.3; N, 4.3%.

EXAMPLE 4

β-[5-(4'-Chlorophenyl)-4-(4'-methoxyphenyl)oxazol-2-yl]propionic acid

The procedure of Example 2(a) was followed, but 4' - chloro - 4 - methoxybenzoin (13.8 g.) of formula



and succinic anhydride (5.5 g.) were reacted for 7 hours at 135—140°C to obtain 4'-chloro - 4 - methoxybenzoin hemisuccinate. Yield 10.8 g. (57.3%).

The procedure of Example 2(b) was then followed, but using this hemisuccinate (9.4 g.), urea (3.6 g.) and glacial acetic acid (25 ml.) to obtain the title compound. Yield 6.7 g. (75.2%), m.p. 130.5—132.5°C.

Analysis: Found: C, 63.75; H, 4.5; N, 3.8; Cl, 9.9. $C_{19}H_{16}ClNO_4$ requires C, 63.8; H, 4.5; N, 3.9; Cl, 10.1%.

Example 5

γ-(4,5-Diphenyloxazol-2-yl)butyric acid

(a) Bezoin (21.2 g.) and glutaric anhydride (11.4 g.) were reacted together following the manner described in Example 1 to yield benzoin hemiglutarate (18.3 g., 56%) as an oil. It had an I.R. spectrum consistent with its structure.

(b) Benzoin hemiglutarate (18.3 g.) and ammonium acetate (30 g.) were heated together in refluxing glacial acetic acid (100 ml.) for 2½ hours. Isolation, as in Example 1 yielded γ - (4,5 - diphenyloxazol - 2 - yl) butyric acid (15.4 g., 89%) as needle crystals, m.p. 125—126°C.

Analysis: Found: C, 74.5; H, 6.0; N, 4.5. $C_{19}H_{17}NO_3$ requires C, 74.3; H, 5.6; N, 4.6%.

Example 6

β-(4,5-Diphenyloxazol-2-yl)propionic acid, ethyl ester

The acid of Example 1 (5 g.) in absolute ethanol (100 ml.) was heated under reflux with concentrated H_2SO_4 (1 ml.) for 16 hours. The mixture was cooled, evaporated *in vacuo* to about 50 ml., and poured into water (200 ml.). The colourless solid formed was filtered, washed with water, sodium bicarbonate, and water again, 5.32 g. The solid was recrystallised from ethanol to give colourless needles of the title compound. Yield 4.4 g. An additional 0.21 g. crystallised from the mother liquors on standing. Total yield 4.61 g. (84.3%), m.p. 69.5—71°C.

Analysis: Found: C, 74.7; H, 6.7; N, 4.4. $C_{20}H_{19}NO_3$ requires C, 74.8; H, 6.0; N, 4.4%.

Example 7

β-(4,5-Diphenyloxazol-2-yl)propionamide

Isobutyl chloroformate (1.23 g.) was added to a stirred suspension of β - (4,5 - diphenyloxazol - 2 - yl)propionic acid (2.5 g.) in a mixture of dry tetrahydrofuran (10 ml.), dry dioxane (10 ml.) and triethylamine (0.85 ml. 9 mM), cooled in ice. The mixture was stirred in ice for 30 minutes and then at room temperature for 1 hour. The mixture was cooled in ice, .880 ammonia (1 ml.) was added in one lot, and stirred for 16 hours. The mixture was poured into water (150 ml.) and the resulting solid collected. Yield 1.7 g. (72%), m.p. 146—7°C after recrystallisation from ethanol.

Analysis: Found: C, 74.2; H, 5.6; N, 9.6. $C_{18}H_{16}N_2O_2$ requires C, 74.0; H, 5.5; N, 9.6.

Example 8

β-[5-(4'-Chlorophenyl)-4-phenyloxazol-2-yl]propionic acid

The procedure of Example 2(a) was followed but 4'-chlorobenzoin (6.2 g.), (i.e. the phenyl ring adjacent to the hydroxy group is substituted) and succinic anhydride (2.75 g.) were reacted at 135—40°C for 6 hours to obtain 4'-chlorobenzoin hemisuccinate. Yield 6.24 g. (69.7%).

The procedure of Example 2(b) was then followed, but using this hemisuccinate (6.24 g.), urea (3.0 g.) and glacial acetic acid (20 ml.) to give the title compound. Yield 3.52 g. (61.7%), m.p. 180—182°C.

Analysis: Found: C, 66.1; H, 4.3; N, 4.1; Cl, 10.7. $C_{18}H_{14}ClNO_3$ requires C, 66.0; H, 4.3; N, 4.3; Cl, 10.8%.

Example 9

β-[5-(4'-Methylphenyl)-4-phenyloxazol-2-]propionic acid

The procedure of Example 2(a) was followed, but 4'-methylbenzoin (11.3 g.), (i.e. the ring adjacent to the hydroxy group is substituted), and succinic anhydride were reacted together at 135—40°C for 5 hours to obtain 4'-methylbenzoin hemisuccinate. Yield 11.0 g. (67.2%).

The procedure of Example 2(b) was then followed, but using this hemisuccinate (7.5 g.), urea (4.1 g.) and glacial acetic acid (20 ml.) to give the title compound. Yield 4.1 g. (63%) m.p. 169—70°C.

Analysis: Found: C, 74.3; H, 5.7; N, 4.6. $C_{19}H_{17}NO_3$ requires C, 74.3; H, 5.6; N, 4.6%.

Example 10

β-[4-(4'-Chlorophenyl)-5-phenyloxazol-2-yl]propionic acid

The procedure of Example 2(a) was followed, but 4-chlorobenzoin (9.9 g.), (i.e. the ring adjacent to the keto group is substituted) and succinic anhydride (4.5 g.) were reacted together for 5 hours at 135—140°C to obtain 4-chlorobenzoin hemisuccinate. Yield 10.5 g. (76%).

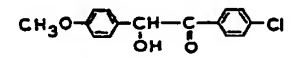
The procedure of Example 2(b) was then followed, but using this hemisuccinate (7.8 g.), urea (3.75 g.) and glacial acetic acid (20 ml.) to give the title compound. Yield 4.16 g. (56.4%), m.p. 155—7°C.

Analysis: Found: C, 65.9; H, 4.3; Cl, 11.4. $C_{18}H_{14}ClNO_3$ requires C, 66.0; H, 4.3; Cl, 10.8%.

Example 11

β-[4-(4'-Chlorophenyl)-5-(4'-methoxyphenyl)oxazol-2-yl]propionic acid

The procedure of Example 2(a) was followed, but 4 - chloro - 4' - methoxybenzoin (10.4 g.) of formula:



and succinic anhydride (4.05 g.) were reacted together at 135—40°C for 5 hours to

obtain 4 - chloro - 4' - methoxybenzoin hemisuccinate. Yield 9.8 g. (67%).

The procedure of Example 2(b) was then followed, but using this hemisuccinate (9.2 g.) to obtain the title compound. Yield 5.0 g. (55.5%), m.p. 126—8°C.

Analysis: Found: C, 63.7; H, 4.6; Cl. 10.05. Calculated for $C_{19}H_{16}ClNO_4$: C, 63.8; H, 4.5; Cl, 10.1%.

Example 12

β-(4,5-Diphenyloxazol-2-yl)propionic acid acetoxymethyl ester

β - (4,5 - Diphenyloxazol - 2 - yl)propionic acid (5.8 g.) was reacted in the presence of triethylamine (2.8 g.) with acetoxymethylbromide (1.84 ml.) in dimethylformamide (50 ml.). The mixture was left overnight at room temperature and then poured into water. The reaction mixture was extracted with ether and the extract washed with water, sodium bicarbonate and then water again before being dried ($MgSO_4$) and evaporated to give a solid. Yield 6.2 g. A further 1.1 g. was obtained on carrying out a second extraction. The product was recrystallised from ethyl acetate to give 5.0 g. (68.1%), m.p. 86—86.5°C.

Analysis: Found: C, 69.2; H, 5.35; N, 4.05. $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%.

Example 13

4-Phenyloxazol-2-ylpropionic acid

Methyl phenacyl succinate (10.0 g.—prepared by heating phenacyl bromide and sodium methyl succinate under reflux in ethanol), urea (6.0 g.) and glacial acetic acid (30 ml.) were heated under reflux for 2 hours. The resulting orange solution was cooled and poured into water (500 ml.). An orange oil formed and solidified after trituration. After filtering off, washing with water and drying, a pale orange sticky solid (6.82 g.) was obtained. This solid was triturated with a small amount of ethanol, the insoluble yellow solid (1.3 g.) removed and the filtrate evaporated to yield 4-phenyloxazol-2-ylpropionic acid as an oil (5.41 g.).

The oil (5.32 g.) in ethanol (100 ml.) was treated with potassium hydroxide (5 g.) in water (10 ml.). The solution was warmed for 10 minutes on a steam bath and then stood at room temperature for 1 hour. After evaporation to low volume, water (50 ml.) was added and the solution extracted with ether (2×50 ml.). The basic aqueous solution was heated with charcoal and acidified to give the title compound as a brown solid (2.93 g.). Recrystallisation of the solid from aqueous ethanol yielded off-white plates (1.63 g.) m.p. 112—6°C. An analytical sample had m.p. 115—7°C.

Analysis: Found: C, 66.0; H, 5.6; N, 6.5. $C_{13}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%.

Example 14

5-Phenyloxazol-2-ylpropionic acid

Finely powdered phenacylamine hydrochloride (5 g.) and dry pyridine (10 ml.) were gently warmed, and β-carbomethoxypropionyl chloride (3 g.) was added, with cooling. Solution was affected by shaking and, after cooling, a further amount of β-carbomethoxypropionyl chloride (2 g.) was added with cooling. After 12 hours at room temperature, iced water was added and the product extracted into ether. The ether extract was washed with saturated sodium hydrogen carbonate, water, dried ($MgSO_4$) and evaporated to give an oil (6.15 g.).

The oil (6.15 g.) was dissolved in concentrated sulphuric acid (10 ml.), left at room temperature for 4 hours and then poured into water. The product was extracted into ether, and the ether extract was washed with water, saturated sodium hydrogen carbonate solution, water, dried ($MgSO_4$) and evaporated to give an oily solid (2.43 g.). I.R. spectra for the product was consistent for methyl 5-phenyloxazol-2-ylpropionate.

The ester (2.43 g.) was dissolved in ethanol (10 ml.) and an alcoholic solution of potassium hydroxide (1 g.) added. The solution was left at room temperature for 2 hours, warmed on a steam bath for 5 minutes and evaporated. The residue was dissolved in water, washed with ether and then acidified to give white crystals of 5-phenyloxazol-2-ylpropionic acid (1.69 g.) m.p. 148—9°C. (Yield 26.5%).

Example 15

β-(4,5-Diphenyloxazol-2-yl)propionic acid	125 mg
Lactose	120 mg
Magnesium stearate	5 mg

Capsules of the above were made up by thoroughly mixing together batches of the above ingredients and filling hard gelatine capsules (250 mg.) with the mixture.

Example 16

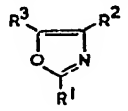
β-(4,5-Diphenyloxazol-2-yl) propionic acid	125 mg
Lactose	100 mg
Avicel (Registered Trade Mark)	30 mg
Dried Maize Starch	40 mg
Magnesium stearate	5 mg

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components and compressing to form tablets.

The active substance in Examples 15 and 16 could be replaced by other of the novel compounds provided by the invention.

WHAT WE CLAIM IS:—

1. Oxazoles of the general formula



and acid addition salts thereof, in which R^1 is a saturated or unsaturated aliphatic carboxylic acid radical containing from 2 to 6 carbon atoms, or a salt, ester, amide or hydroxamic acid derivative thereof, said carboxylic acid radical or salt, ester, amide or hydroxamic acid derivative being attached to the oxazole ring by a carbon atom of the aliphatic chain, at least one of R^2 and R^3 is a substituted or unsubstituted aryl group (which may be a heteroaryl group) and the other radical R^2 or R^3, if not a substituted or unsubstituted aryl group (which may be a heteroaryl group) is a hydrogen atom or an alkyl group, with the proviso that, when R^3 is a hydrogen atom and R^2 is a phenyl radical which may optionally be substituted by not more than two halogen atoms or by a trifluoromethyl radical, then R^1 contains at least two carbon atoms in a straight chain between the oxazole ring and the carboxyl group or salt, ester, amide or hydroxamic acid derivative thereof.

2. Oxazoles of the general formula given in Claim 1, wherein R^1 is a saturated or unsaturated aliphatic acid radical containing from 2 to 4 carbon atoms or a salt, ester, amide or hydroxamic acid derivative thereof, said carboxylic acid radical being attached to the oxazole ring by a carbon atom of the aliphatic chain.

3. Oxazoles as claimed in Claim 2, wherein the aliphatic acid radical is that derived from *n*-propionic, iso-propionic, *n*-butyric or acrylic acid.

4. Oxazoles as claimed in Claim 2 or Claim 3, wherein R^2 and R^3 each is a phenyl, substituted phenyl, naphthyl, furyl or thienyl radical.

5. Oxazoles as claimed in Claim 4, wherein R^2 and R^3 each is phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, trifluoromethylphenyl, 1-naphthyl, 2- or 3-furyl or 2- or 3-thienyl, and "lower" means the radicals contain up to 6 carbon atoms.

6. Oxazoles as claimed in Claim 5, wherein R^2 and R^3 each is phenyl, chlorophenyl, bromophenyl, methylphenyl or methoxyphenyl.

7. β - (4,5 - Diphenyloxazol - 2 - yl) propionic acid.

8. β - [4,5 - Di - (4′ - methoxyphenyl) oxazol-2-yl] propionic acid.

9. β - [4 - (4′ - Methoxyphenyl) - 5 - phenyloxazol-2-yl] propionic acid.

10. β - [5 - (4′ - Chlorophenyl) - 4 - (4′-methoxyphenyl)oxazol-2-yl] propionic acid.

11. γ - (4,5 - Diphenyloxazol - 2 - yl) butyric acid.

12. β - (4,5 - Diphenyloxazol - 2 - yl)propionic acid ethyl ester.

13. β - (4,5 - Diphenyloxazol - 2 - yl)propionamide.

14. β - [5 - (4′ - Chlorophenyl) - 4 - phenyloxazol-2-yl] propionic acid.

15. β - [5 - (4′ - Methylphenyl) - 4 - phenyloxazol-2-yl] propionic acid.

16. β - [4 - (4′ - Chlorophenyl) - 5 - phenyloxazol-2-yl]propionic acid.

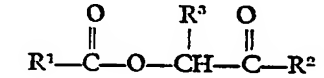
17. β - [4 - (4′ - Chlorophenyl) - 5 - (4′ - methoxyphenyl)oxazol - 2 - yl] propionic acid.

18. β - (4,5 - Diphenyloxazol - 2 - yl)propionic acid acetoxymethyl ester.

19. 4 - Phenyloxazol - 2 - ylpropionic acid.

20. 5 - Phenyloxazol - 2 - ylpropionic acid.

21. A process for the preparation of compounds of the general formula given in Claim 1, in which R^1 is an aliphatic acid radical containing 2 to 6 carbon atoms, or an ester thereof which comprises reacting a ketoester of the general formula



with ammonia or a salt thereof, or urea, (where R^2 and R^3 have the meanings defined in Claim 1 and R^1 has the meaning defined above).

22. A process as claimed in Claim 21, wherein R^1 contains 2 to 4 carbon atoms and wherein the reaction is carried out by heating with ammonium acetate in glacial acetic acid.

23. A process as claimed in Claim 22, wherein benzoin hemisuccinate ester is cyclised.

24. A process as claimed in Claim 23, substantially as described with reference to Example 1.

25. A process as claimed in Claim 21, substantially as described with reference to any of Examples 2 to 5 or 8 to 11.

26. A process for the preparation of a compound of the general formula given in Claim 1, in which R^1 is an aliphatic acid amide radical containing 2 to 6 carbon atoms and R^2 and R^3 have the meanings defined in Claim 1, which comprises reacting the corresponding acid with an alkyl haloformate followed by reaction with ammonia.

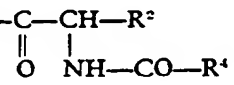
27. A process as claimed in Claim 26, substantially as described with reference to Example 7.

28. A process for the preparation of a compound of the general formula given in Claim 1, in which R^1 is an alkyl ester or an acyloxymethyl ester derivative of an acid radical containing 2 to 6 carbon atoms and R^2 and R^3 have the means defined in Claim 1, which

comprises reacting the corresponding acid with an alkanol or an acyloxymethyl halide respectively.

29. A process as claimed in Claim 28, substantially as described with reference to Examples 6 or 12.

30. A process for the preparation of a compound of the general formula given in Claim 1, which comprises cyclising an α-acylamino ketone of the general formula



and if necessary converting R^4 to R^1, (where R^1, R^2 and R^3 have the meanings defined in Claim 1, and R^4 has the same meaning as R^1 or is a radical convertable thereto).

31. A process as claimed in Claim 30, wherein cyclisation is effected by treatment with sulphuric acid, phosphorus pentachloride, phosphoryl chloride or phosphorus pentoxide.

32. Compounds of the general formula given in Claim 1, when prepared by the process claimed in any of Claims 21 to 31.

33. A pharmaceutical composition comprising a compound as claimed in Claim 1 and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising a compound as claimed in any of Claims 2 to 6 and a pharmaceutically acceptable carrier.

35. A pharmaceutical composition comprising a compound as claimed in Claim 7 and a pharmaceutically acceptable carrier.

36. A pharmaceutical composition comprising a compound as claimed in any of Claims 8 to 11 and a pharmaceutically acceptable carrier.

37. A pharmaceutical composition comprising a compound as claimed in any of Claims 12 to 20 and a pharmaceutically acceptable carrier.

38. A pharmaceutical composition substantially as described with reference to Example 15 or 16.

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